REMARKS/ARGUMENTS

Status of Claims

Prior to entry of this paper, claims 1, 3, 5, 8-10, 14-15, 35-42, and 45 were canceled, and claims 2, 4, 6-7, 11-13, 16-34, 43-44, and 46-52 were pending. Claims 16-17, 28-31, and 33-34 were withdrawn by the Examiner.

With entry of this paper, claims 6, 11-13, 16-17, 28, 30-31, and 44 are canceled; claims 2, 4, 43, 46, and 47 are amended; and new claims 53 and 54 are added.

After entry of this paper, claims 1, 3, 5-6, 8-17, 28, 30-31, 35-42, and 44-45 are canceled, and claims 2, 4, 7, 18-27, 29, 32-34, 43, and 46-54 are pending. Claims 29 and 33-34 are withdrawn by the Examiner.

Applicants reserve the right to pursue one or more continuations, divisionals, or continuations-in-part to any canceled subject matter.

Support for Amendments

The Abstract is amended to include the term "NO:" as directed by the Office Action to correct an obvious typographical error.

The specification is amended at pages 21 and 50 to correct obvious grammatical errors, and to correct a typographical error by replacing the chemical term "methyl" with the chemical term "ethyl," and to correct a typographical error in the term "SacE" with "SacF." Support for the chemical term "ethyl" can be found in the chemical drawing of P3 as shown in Figure 8, which requires that the chemical names on pages 21 and 50 be amended in order to be correct. Support for "SacF" can be found in Example 6, which specifies the SacF mutant.

Claims 2, 4, and 43 are amended and new claim 53 is added to present various embodiments related to SEQ ID NO:1 consistent with the Restriction Requirement of August 1, 2006 and with the scope of examination to date. Applicants believe the amendments place the claims in condition for allowance or in better form for Appeal. Support for the amendment can be found throughout the specification as filed, for example in Example 3, pages 29-31.

Claims 46 and 47 are amended to correct the claim dependencies according to US patent practice, and to correct a typo on claim 46.

New claim 54 is added to present an embodiment of claim 25. Support can be found in the specification at paragraphs 21-22 of the application as published.

No new matter is entered.

No New Issues Are Raised by Entry of the Amendments

Applicants respectfully request entry of the amendments as they raise no new issues for consideration and they simplify matters for possible appeal. For example, the *sacABCDEFGH* operon was already present in claim 43. Therefore, amending claim 2 to include the *sacABCDEFGH* operon presents no new issues for consideration. In addition, entry of the amendment simplifies matters for possible appeal by removing issues such as the interpretation of "contiguous portion" from claim 2 or the interpretation of "stringent conditions" from claims 11-13. New claims 53 and 54 present no new issues, as claim 53 presents an embodiment of claim 2 in independent form, and claim 54 presents an embodiment of claim 25.

Objection to the Specification

In response to the objection to the specification, the term "NO:" is inserted in the Abstract as suggested in the Office Action. Applicants respectfully request withdrawal of the objection.

Request for an Update to the USPTO's Electronic Application Data

Applicants' previous attempts to prompt correction of the USPTO's electronic application data to include the priority claim to GB 0229793.5 (filed December 20, 2002) have apparently been unsuccessful. The priority claim has been acknowledged in the previous Office Actions, and Applicants thank the Examiner for indicating that the Examiner would contact OIPE to resolve the clerical problem (see Office Action, page 13, line 9). As of the date of this response, Applicants note that the USPTO's electronic application data has not yet been corrected. Applicants respectfully request correction of the USPTO's records and an updated Filing Receipt to acknowledge the correction.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 11-13 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Applicants respectfully traverse. However, upon entry of this paper, claims 11-13 are canceled. Applicants respectfully request withdrawal of the rejection as being moot.

Rejection Under 35 U.S.C. § 102(b)

Claims 2, 4, 6-7, 18-22, 24-27, 32, and 43-44 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pospiech et al. (Microbiology, vol. 141, pages 1793-1803, February 18,

1999) based on the broad recitation of variant or portion thereof. By amendment, the recitation of variant or portion thereof was previously removed from the claims. The Office Action maintains the rejection, arguing that the previous amendments "were not sufficient to obviate this ground of rejection. The claims still read broadly on any fragment or variant thereof" (Office Action, page 13, lines 5-8).

Applicants respectfully traverse on the basis that the rejection appears to be moot. Simply put, the terms "fragment" or "variant thereof" do not occur in the claims filed in response to the previous Office Action. In addition, Applicants have been unable to find the allegedly anticipatory content of Pospiech, and the Office Action fails to point out the content of Pospiech which allegedly anticipates the claims filed in response to the previous Office Action.

Moreover, in order to advance prosecution, the phrase "contiguous portion of SEQ ID NO:1" has been removed from claim 2, as well as phrase "e)" referring to a nucleic acid sequence encoding a variant of the non-ribosomal peptide synthetases SacA, SacB or SacC. Therefore, Applicants respectfully request that the rejection be withdrawn, or, in the alternative, that the Examiner at least provides the nucleotide sequence in Pospiech that allegedly anticipates the instant claims.

Rejection Under 35 U.S.C. § 112, first paragraph- enablement

Claims 2, 4, 6-7, 11-13, 18-27, 32, 43-44, and 46-52 (all pending, non-withdrawn claims) are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement for the entire scope of the claims. Applicants respectfully traverse the rejection.

With respect to arguments directed to primers or probes, Applicants note that claims 11-13 are canceled upon entry of this paper. Therefore, the arguments with respect to primers or

probes are moot. Similarly, the arguments with respect to the term "portion" are irrelevant in view of the amendments submitted in this paper.

The Office Action states that the claims are directed to "a nucleic acid" and "a contiguous portion of SEQ ID NO:1," and then argues that the claims recite open language "comprising," thus the "claims encompass a large variable genus of variants/derivatives based on the aforementioned language" (Office Action, page 4, lines 13-16). The Office Action further states that due to "the large quantity of experimentation necessary to generate the infinite number of variants/derivatives recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation," (Office Action, page 4, lines 18-22).

It is unclear to Applicants how the Office Action arrives at an "infinite" number of variants/derivatives. If the term "comprising" is the issue, Applicants assert that an interpretation of "comprising" as somehow generating an "infinite" number of variants/derivatives that must each be tested and analyzed would be inconsistent with US case law that explicitly permits the use of "comprising" as a transitional phrase. See, for example, *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948), where it was acknowledged that "comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts." See also MPEP 2111.03. A reading of the open nature of the term "comprising" as requiring that any possible embodiment, no matter how far-fetched, be reduced to practice in order to comply with the enablement requirement is inconsistent with the case law. In other words, the Office Action's reliance on "comprising" as somehow generating an "infinite" number of

variants/derivatives goes against long-standing patent practice, and is therefore an unreasonably broad interpretation of the term.

In any event, Applicants respectfully traverse the rejection on the basis that the specification provides clear guidance with respect to the scope of the claims. Guidance for each of the elements of a) the nucleic acid sequence SEQ ID NO:1; or b) the sacABCDEFGH operon of SEQ ID NO:1; or c) the *sacA*, *sacB*, *sacC*, *sacD*, *sacE*, *sacF*, *sacG*, and *sacH* genes of SEQ ID NO:1; or d) the nucleic acid sequence encoding the SacA, SacB, SacC, SacD, SacE, SacF, SacG, and SacH proteins (SEQ ID NO:2-9) encoded in SEQ ID NO:1; or e) the nucleic acid sequence which is the full complement to the sequence in a), b), c), or d); are each clearly provided in the specification. For example, see the guidance on the structure and function of the *sacA* to *sacH* genes contained in the sacABCDEFGH operon of SEQ ID NO:1, that is provided in the specification at page 29, last paragraph through page 31, first paragraph.

The Office Action argues that the claim language "reads on any fragment or variant of the disclosed SEQ ID NO:1 which has 26705 nucleotides. Therefore, no correlation has been made been[sic] structure and function" (Office Action, page 5, lines 6-8). Applicants respectfully traverse on the basis that the Office Action presents an unreasonably broad interpretation of the claims, where the terms "fragment" and "variant" simply do not appear. As noted above, the phrase "contiguous portion of SEQ ID NO:1" has been removed from claim 2, as well as phrase "e)" referring to a nucleic acid sequence encoding a variant of the non-ribosomal peptide synthetases SacA, SacB or SacC. Therefore, Applicants respectfully request that the rejection be withdrawn.

With regard to the Office Action's discussion of Seffernick (J. Bacteriology, vol. 183, pages 2405-2410, 1001), the Office Action's conclusions are actually entirely inconsistent with

the teachings of Seffernick. The Office Action relies on Seffernick to support the conclusion that "the state of the art provides evidence for the high degree of unpredictability as stated above" (Office Action, page 5, lines 16-17). On the contrary, Seffernick provides a single exception to the rule, and specifically teaches that "it is surprising that enzymes with such high sequence identity catalyze different reactions" (Seffernick, page 2409, left column, lines 39-40). Moreover, Seffernick categorically states that the finding "that proteins with >98% sequence identity catalyze different reactions in different metabolic pathways is **highly exceptional**" (Seffernick, page 2409, left column, lines 22-26, emphasis added). In fact, Seffernick teaches the exact opposite of what the Office Action would like to conclude, *i.e.*, according to the state of the art, genome annotation with "functional assignments based on >50% sequence identity are considered to be reasonably sound" (Seffernick, page 2409, left column, lines 22-26, emphasis added). Thus, the Office Action's statements with respect to the state of the art and lack of predictability are not even supported by the Office Action's own cited art.

In the specification of the present invention, Applicants have identified the genes responsible for safracin production in *Pseudomonas fluorescens*, and performed gene disruption analysis to determine the function of the cloned genes, while also identifying aspects of the biosynthetic pathway and producing new safracin-like compounds (see Examples 2-7). Applicants have shown that the complete sequence SEQ ID NO:1 is not necessary to obtain safracin compounds. Rather, specific examples are provided where some of the individual genes in SEQ ID NO:1 have been disrupted, leading to the synthesis of natural safracins or safracin analogs. See Figure 6, which summarizes the functional analysis in Example 4. In other words, when considered in conjunction with the state of the art, Applicants have provided detailed guidance commensurate in scope with the claims such that the instant claims are enabled.

Accordingly, Applicants respectfully request withdrawal of the rejection for lack of enablement.

Rejection Under 35 U.S.C. § 112, first paragraph- written description

Claims 2, 4, 6-7, 11-13, 18-27, 32, 43-44, and 46-52 (all pending, non-withdrawn claims) are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Applicants respectfully traverse the rejection.

With respect to arguments directed to primers or probes, Applicants note that claims 11-13 are canceled upon entry of this paper. Therefore, the arguments with respect to primers or probes are moot. Similarly, the arguments with respect to the term "portion thereof" are irrelevant in view of the amendments submitted in this paper.

The Office Action argues that the claims are directed to a genus of nucleic acids and proteins that are not adequately described "as a skilled artisan cannot envision the detailed chemical structure of the derivatives encompassed in the claims" (Office Action, page 8, lines 8-10).

New claim 2 is directed to an isolated nucleic acid sequence comprising a) the nucleic acid sequence SEQ ID NO:1; or b) the sacABCDEFGH operon of SEQ ID NO:1; or c) the *sacA*, *sacB*, *sacC*, *sacD*, *sacE*, *sacF*, *sacG*, and *sacH* genes of SEQ ID NO:1; or d) the nucleic acid sequence encoding the SacA, SacB, SacC, SacD, SacE, SacF, SacG, and SacH proteins (SEQ ID NO:2-9) encoded in SEQ ID NO:1; or e) the nucleic acid sequence which is the full complement to the sequence in a), b), c), or d).

In the specification of the present invention, Applicants have identified the genes responsible for safracin production in *Pseudomonas fluorescens*, and performed gene disruption

analysis to determine the function of the cloned genes, while also identifying aspects of the biosynthetic pathway and producing new safracin-like compounds (see Examples 2-7). In addition, Applicants have shown that the complete sequence SEQ ID NO:1 is not necessary to obtain safracin compounds. Rather, specific examples are provided where some of the individual genes in SEQ ID NO:1 have been disrupted, leading to the synthesis of natural safracins or safracin analogs. See Figure 6, which summarizes the functional analysis in Example 4. The disruption of orf1, orf2, orf3 and orf4 leads to the isolation of P2, P14, Safracin A, and Safracin B. The disruption of sacI gene (SacI- mutant) leads to the isolation of P2, P14 and P19B. The disruption of sacJ gene (SacJ- mutant) leads to the isolation of P2, P14, P19B, P22A and P22B. Interestingly, the disruption of the genes sacA, sacB, sacC, sacD, sacF and sacG does not allow the isolation of the precursor compounds: P2 or P14, nor does it lead to the isolation of a safracin compound. See specification, page 33, lines 13-17. On the other hand, on pages 44 to 47 the specification shows that the disruption of SacI gene with sacJ gene reconstitution leads to the isolation of the new safracin compounds Safracin D and Safracin E.

Accordingly, in the present specification, several examples of nucleic acid sequences which comprise the sacABCDEFGH operon and lead to the isolation of safracin compounds (*i.e.*, natural safracins and safracin analogs) have been provided.

Furthermore, according to the functional assays of the gene knock out mutants provided in Example 4, the sacI and sacJ genes encoded in the sacIJ operon have a well defined function. SacI encodes a methyl-transferase and SacJ a monooxygenase (see Table I, linking pages 18-19). The expression of said genes entails specific modifications in the safracin structure (*i.e.*, N-methylation and/or the presence of the quinone ring). Thus, it is shown in the specification that different safracin compounds will be obtained depending on the presence/absence of these genes.

Therefore, Applicants submit that several species of the claimed genus are provided in the specification, which share a common function (*i.e.*, providing for the biosynthesis of safracin compounds).

As seen above, Applicants submit that in the specification as filed it has been shown that SEQ ID NO:1 or the sacABCDEFGH operon or a nucleic acid sequence comprising the genes contained therein or a nucleic acid sequence coding for the SacA to SacH proteins encoded in the sacABCDEFGH operon are sufficient to achieve the biosynthesis of a safracin compound. Therefore, as presently claimed, Applicants have provided both structure and function sufficient to meet the written description requirement.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105008. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105008.

Respectfully submitted,
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Dated: December 19, 2008

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